

Olfactory Neuroblastoma in Northern Thailand

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Abstract: Two cases of olfactory neuroblastoma in women in northern Thailand are described. Original complaints were severe headaches and eye pain; death occurred from intracranial extensions 6 months and 1 year after diagnosis. Results of study with light microscopy, immunohistopathology, and electron microscopy are reviewed, and several management recommendations are discussed. **Jpn J Ophthalmol 1997;41:27-30** © 1997 Japanese Ophthalmological Society

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Introduction

Olfactory neuroblastoma (ON), or esthesioneuroblastoma, is a specific variant of neuroblastoma arising from neuroepithelial elements in the olfactory placode.^{1,2} Classified as a rare tumor, it was first reported by French ophthalmologist Berger in 1924. It has a wide age distribution (3-88 years old), although most patients are between 15 and 40 years old.³⁻⁵ The tumor is very invasive and usually not truly metastatic, although cervical lymph nodes or lungs may be involved.⁶ Signs and symptoms are directly related to the location and extension of the disease. When localized in the nasal cavity, the tumor causes unilateral nasal obstruction, frequent epistaxis, and rhinorrhea. Orbital extension causes excessive lacrimation, retrobulbar pain, proptosis, blurring, or loss of vision. Because of its strongly invasive character, the tumor can extend to nearby structures and into the cranium.^{6,7} Intracranial extension is indicated by nausea and vomiting, meningism, and personality changes. This article describes two cases of ON in women in northern Thailand, who presented with ocular symptoms.

Case Reports

Medical records of two cases of olfactory neuroblastoma were examined. Histopathologic and immunohistopathologic studies were done with a light microscope; paraffin-embedded sections were further processed for electron-microscopic study (Transmission electron microscope 1200EX II, JEOL, Tokyo).

Patient 1

A 58-year-old Thai woman first visited this hospital in October 1990. She had been unable to move her left eye horizontally for 2 weeks and had ptosis of the eye for 1 week. She reported experiencing episodes of severe left eye pain and a foul smell in the left nostril for the previous year and had been admitted twice to a private hospital. On the first admission, a skull computed tomography (CT) scan was false-negative, and she was treated for migraine and hypertension. Because of an increased blood erythrocyte sedimentation rate (ESR), she received treatment for temporal arteritis on the second admission. Pain diminished slightly, but never completely disappeared.

Examination in our clinic revealed mild complete proptosis; paresis of the horizontal muscles of the left eye. Visual acuities were 6/9, 6/24; visual field was normal with 4 mm dilatation in left pupil; there was slight reactivity to light, but consensual light reflex was negative. Cervical lymph nodes were not enlarged; nasopharynx and inferior oropharynx were normal. Gynecologic examination was negative. ESR

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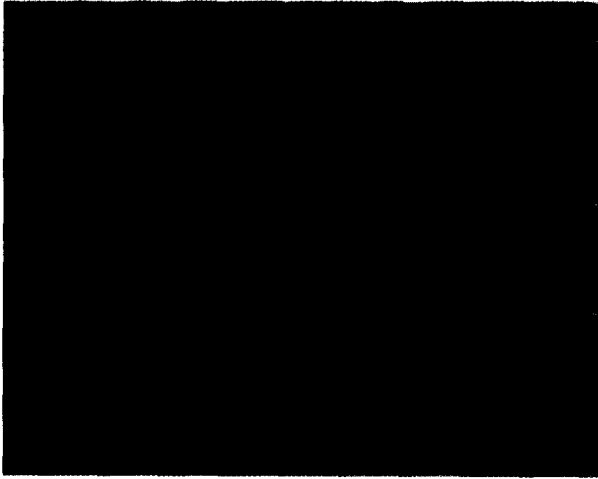


Figure 1. *Case 1:* The histoimmunology, S-100 positive staining as pinkish material in the cytoplasm, nucleus (black arrow), and cytoplasmic process of the cells (white arrow) ($\times 1,000$).

was 6 at 30 minutes, 30 at 60 minutes. Venereal Disease Research Laboratories (VDRL) test was negative. Fasting blood sugar was 98 mg%. IgA, IgM, and IgG were within normal ranges. Plain skull X-rays, lateral and superior orbital fissure views, revealed destruction of the sella turcica. A skull CT scan revealed a large mass affecting the cervical spine at C1, C2, and extending into the sphenoid sinus to the sella turcica. Only one, from the sphenoid sinus, of the many biopsies done was suggestive of ON. Histopathologically, an HE stain revealed cords of tumor cells slightly larger than lymphocytes among the fibrillary structures. Pseudorosettes and true rosettes were occasionally seen. Immunohistopathologically, S-100 protein was positive, staining pink in the cyto-



Figure 2. *Case 1:* Electron micrograph showing numerous cytoplasmic processes (black arrow) among Nissl's bodies (white arrow) ($\times 20,000$).

plasm and nucleus, and extending into the intercellular spaces around other tumor cells (Figure 1). Glial fibrillary acidic protein (GFAP) was negative. In ultramicroscopic examination: cytoplasm was poorly differentiated, except for abundant free ribosomes, with scant organelles (Figures 2 and 3). The prominent feature was the presence of dense core vesicles ranging from 100–160 nm in diameter; although there were only a few, they were scattered throughout the cytoplasm. Numerous cytoplasmic processes, probably dendritic processes, were seen (Figure 2).

The patient later developed severe lumbar pain. A bone scan showed multiple sites of increased uptake at the medial end of T12, the right sternoclavicular joint and ribs, indicating multiple bone metastases. Chest x-ray showed multiple osteolytic lesions of the ribs and alveolar infiltration of the right lower lung field.

She was admitted to this hospital on February 8, 1991; treatment was symptomatic and supportive only. She developed confusion, restlessness, severe left periorbital and lumbar pain and rectal bleeding, and died on February 11, 1991, from the intracranial extension.

Patient 2

A 16-year-old woman visited this hospital on January 5, 1993, complaining of severe headache and left eye pain of 1 week's duration, and loss of sight in the left eye for the previous 4 days. Visual acuities were 6/12, FL 0.15 m. Ocular tensions were 10 and 18 mm Hg. There was paresis of the left lateral and medial rectus muscles, with slight weakness of the superior and inferior rectus muscles. The left pupil diameter was 3 mm; it was sluggishly reactive to light. Fundus examination found no papilledema bi-

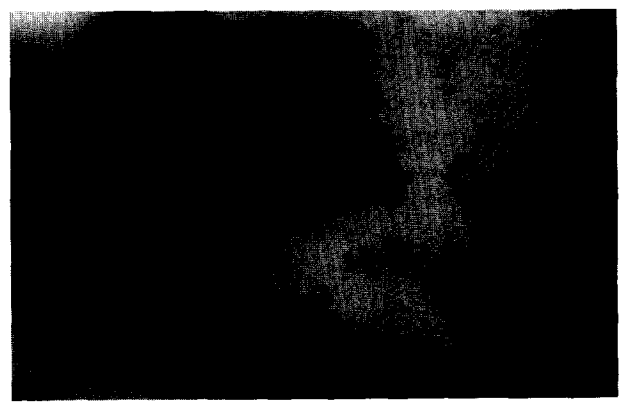


Figure 3. *Case 1:* Electron micrograph showing the dense core vesicles consisting of neurotransmitters in the vesicles (black arrow) ($\times 150,000$).

laterally. On January 8, her tongue deviated to the right and pain became more severe. On examination of the nasopharynx and ears, nothing exceptional was found, but there was numbness on the left side of the face, which is supplied by the second division of the fifth cranial nerve. X-rays of the paranasal sinuses revealed clouding of the left ethmoid air cell; a skull CT scan on January 8 showed an enhancing mass in the posterior air cells of the left antrum with destruction of the lateral wall, resulting in extension of the mass into the extraconal area of the left orbital apex. The optic nerve was compressed and deviated laterally. Carcinoma of the posterior air cells of the left ethmoid was suspected; exploratory craniofacial surgery on January 27 exposed posterior ethmoid tumors involving the apex of the left orbit, left middle turbinate, and anterior ethmoid, which could not be completely removed. Histopathologically, HE staining showed a cord of small cells among the fibrillary structure (Figure 4). Immunohistopathologically, S-100 was slightly positive and GFAP was negative. Most ultramicroscopic findings were similar to those of Patient 1. The nucleus was more pleomorphic, forming multiple pockets; the nucleolus was visible in some cells. Neurofibrils were scattered in the cytoplasm and cytoplasmic processes of the tumor cells (Figure 5).

This patient was discharged from the hospital after 23 days without receiving any radiation therapy. Six weeks postoperatively, a repeat CT scan of the skull revealed advanced recurrent masses in the left orbit and left nasal cavity, with intracranial extension and destruction of the sella turcica. Three weeks later, she developed severe periorbital pain and proptosis of the left eye with exposure keratitis; there was no



Figure 4. Case 2: The histopathologic section H/E stain showing sheets or cords of the tumor cells among the fibrillary structures (white arrow) ($\times 1,000$).

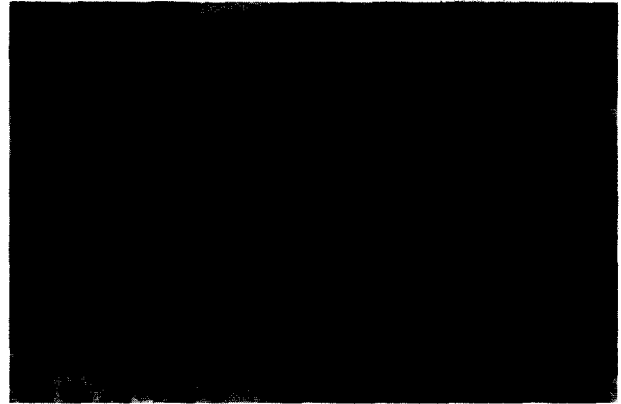


Figure 5. Case 2: Electron micrograph showing numerous dense core vesicles (white arrow), and neurofibrils (black arrow) in the cytoplasm of the tumor cell ($\times 50,000$).

light perception. She died of intracranial extension on April 19, 1993.

Discussion

On initial visit to our clinic, the first patient complained of severe left eye pain. Diagnosis and treatment had been delayed because of an earlier false-negative CT scan. Additionally, we encountered difficulty in obtaining tissue for histopathologic examination since there was no gross tumor mass in the nasal cavity or nearby sinuses. Tumor spread was most probably via the submucosa into the upper cervical spine, entering the skull via the subdural space and resulting in severe headache. The second patient had a short history of severe headache and loss of vision in the left eye. Surgery was done early, but the tumor mass had already spread into the surrounding sinuses and the left orbit and could not be completely removed. Many researchers have recommended postoperative radiation or chemotherapy in such a situation,^{6,8-12} however, this patient received neither and died of intracranial tumor extension 5 weeks postoperatively.

Since this tumor is very rare, originating from the primitive neuroectomal cell element of the olfactory placode, it is often misdiagnosed as transitional cell carcinoma, reticulum cell sarcoma, malignant melanoma, aplastic carcinoma, or rhabdomyosarcoma. Using only the light microscope for histologic examination can lead to misdiagnosis; sheets of small cells, larger than lymphocytes and surrounded by fibrillary stroma, round or oval nuclei and fine or coarse chromatin could resemble these other tumors.⁴ Immunohistology is helpful in accurate diagnosis of this rare tumor, assessing neurospecific enolase, S-100 pro-

tein, GFAP, and the beta-globulin isotype. Both patients in our case reports had positive S-100 protein, but were negative for GFAP. These studies must be regarded only as helpful adjuncts in diagnosis; the substances evaluated are not unique to neural and neuroendocrine tumors, but can also be found in other tumors.¹²⁻¹⁴

The most useful technique for definitive diagnosis of olfactory neuroblastoma is electron microscopy. A number of reports have detailed the ultrastructural features of ON.^{10,11,13,15-17} The presence of abundant axons, dense core vesicles of various sizes, numerous cytoplasmic processes, microtubules, and synaptic complexes are indicative of the neuronal nature of the neoplasm. We saw, in our patients, the dense core granules, cleared center vesicles, compact bundles of cytoplasmic filaments (presumably neurofilaments), Nissl bodies—all typical of the recognized characteristics of ON. A cilia-like structure was seen in the second patient, suggesting partial differentiation toward olfactory epithelium. The nucleus of the tumor cells in the second patient was more convoluted; in the first patient, it was more rounded. This may explain the more aggressive nature of the tumor in the younger patient.^{4,18} We have demonstrated that the findings in our cases are consistent with ON.

There has been a relatively large number of reports describing the clinical course of ON. Men and women were equally represented in the bimodal age distribution. Kadish¹¹ divided patients into three groups: group A, with tumor only in the nasal cavity; group B, with tumor in the nasal cavity and the sinus of the same side; and group C, with tumors that have invaded the cranium or orbit. He recommends radiotherapy prior to surgery for groups A and B, and radiotherapy and surgery for group C. Both our patients would probably be in group B; early diagnosis was possible only in the second. Difficulty of diagnosis, with resulting delay in treatment, affects the death rate.¹⁵ Diagnosis should not rely on histopathologic examination alone since ON may be mistaken for many other tumors. The most effective diagnostic aid is the electron microscope. In addition,

with this type of tumor, lifetime follow-up is mandatory: there is no 5-year survival rate with ON; it can recur even after 10-15 tumor-free years.

References

1. Chaudry AP, Harr JG, Koul A, Nickerson PA. A light and ultrastructural study of two cases. *Cancer* 1979;44:564-79.
2. Oberman HA, Rice DH. Olfactory neuroblastoma: A clinicopathological study. *Cancer* 1976;38:2497-502.
3. Schall LA, Lineback M. Primary intranasal neuroblastoma. *Ann Otolaryngol* 1972;60:221-29.
4. Schenck NL, Ogura JH. Esthesioneuroblastoma: An enigma in the diagnosis, a dilemma in treatment. *Arch Otolaryngol* 1972;96:322-24.
5. Woodhead P, Lloyd GA. Olfactory neuroblastoma: Imaging by magnetic resonance, CT and conventional techniques. *Clin Otolaryngol* 1988;13(5):387-94.
6. Seaman WB. Olfactory esthesioneuroepithelioma. *Radiology* 1951;57:541-46.
7. Choi HS, Anderson PL. Immunohistochemical diagnosis of olfactory neuroblastoma. *J Neuropathol Exp Neurol* 1985;44(1):18-31.
8. Appelblatt NH, Mc Clatchy. Olfactory neuroblastoma: A retrospective clinicopathologic study. *Head Neck Surg* 1982;5(2):108-13.
9. Becker MH, Jacox HW. Olfactory esthesioneuroepithelioma. *Radiology* 1964;82:77-83.
10. Grahne B. Olfactory neuroblastoma. *Acta Otolaryngol* 1965;59:59-64.
11. Kadish S, Boodmann M, Wang CC. Olfactory neuroblastoma: A clinical analysis of 17 cases. *Cancer* 1976;37:1571-76.
12. Steven A, Francis P, Kuhajda. Esthesioneuroblastoma intermediate filament, neuroendocrine, and tissue-specific antigens. *Am J Clin Pathol* 1987;88(2):139-45.
13. Fitz-Hugh GS, Allen MS Jr, Rucker TN, Sprinkle PM. Olfactory neuroblastoma. *Arch Otolaryngol* 1965;81:161-68.
14. Frieson HF Jr, Ross GW, Mills SE. Olfactory neuroblastoma. Additional immunohistochemical characterization. *Am J Clin Pathol* 1990;94:547-53.
15. Obert GJ, Devine KD, Mc Donald JR. Olfactory neuroblastoma. *Cancer* 1960;13:205-15.
16. Tamada A, Makimoto K, Okawa M, Hirono Y, Yamabe H. Olfactory neuroblastoma: Presentation of a case and review of the Japanese literature. *Laryngoscope* 1984;94:252-56.
17. Weiden PL, Yarrington CT Jr, Richardson RG. Olfactory neuroblastoma chemotherapy and radiotherapy for extensive disease. *Arch Otolaryngol* 1984;110(11):759-60.
18. Du ZM, Li YS, Wang BF. Electron microscopic and immunohistochemical findings in a case of olfactory neuroblastoma. *J Clin Pathol* 1993;46:83-85.